

## Clinical reviews in allergy and immunology

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# Chronic granulomatous disease: Overview and hematopoietic stem cell transplantation

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Chronic granulomatous disease (CGD) still causes significant morbidity and mortality. The difficulty in considering high-risk yet curative treatments, such as allogeneic bone marrow transplantation, lies in the unpredictable courses of both CGD and bone marrow transplantation in different patients. Some patients with CGD can have frequent infections, granulomatous or autoimmune disorders necessitating immunosuppressive therapy, or both but also experience long periods of relative good health. However, the risk of death is clearly higher in patients with CGD of all types, and the complications of CGD short of death can still cause significant morbidity. Therefore, with recent developments and improvements, bone marrow transplantation, previously considered an experimental or high-risk procedure, has emerged as an important option for patients with CGD. We will discuss the complications of CGD that result in significant morbidity and mortality, particularly the most common infections and autoimmune/inflammatory complications, as well as their typical management. We will then discuss the status of bone marrow transplantation. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

**Key words:** Chronic granulomatous disease, infection, inflammation, autoimmune, allogeneic hematopoietic transplantation

Chronic granulomatous disease (CGD) results from defects in the reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, resulting in an inability to produce the superoxide anion necessary for normal killing of bacterial and fungal microorganisms. In addition, this defect predisposes to granulomatous complications and autoimmune diseases. Mutations in at least 5 different genes involved in the assembly and activation of the NADPH oxidase can lead to CGD.<sup>1</sup> The gene encoding the enzymatic center of the NADPH oxidase, gp91<sup>phox</sup>, is on the X-chromosome and accounts for about two thirds of the cases. Autosomal forms occur from mutations in p47<sup>phox</sup>,

### Abbreviations used

ATG: Antithymocyte globulin  
CGD: Chronic granulomatous disease  
GvHD: Graft-versus-host disease  
NADPH: Nicotinamide adenine dinucleotide phosphate  
NIH: National Institutes of Health

p67<sup>phox</sup>, p22<sup>phox</sup>, or p40<sup>phox</sup>, with the latter being the most recently described.<sup>2</sup> In general, gp91<sup>phox</sup>-deficient patients (ie, those with X-linked CGD) are the most severely affected, whereas patients with mutations in p47<sup>phox</sup> seem to have the best outcomes overall. Deficiency in p40<sup>phox</sup> might predispose to more gastrointestinal disease and fewer infections.<sup>2</sup> Specific mutations affect the severity of disease through the amount of residual NADPH oxidase activity.<sup>3</sup> However, even among patients with similar NADPH oxidase mutations, there can be widely different clinical outcomes. Therefore the genetic type of CGD, the specific mutation, the patient's own infection history, the presence of inflammatory or autoimmune complications, and access to appropriate medical care all factor into what to expect from CGD in a particular patient's case.

## INFECTION

Despite the significant progress made in antibiotic and antifungal therapy and prophylaxis, patients with CGD still have serious infections. Most large studies have shown an infection rate of around 0.15 to 0.3 per year.<sup>4-6</sup> The US National Institutes of Health (NIH) has followed more than 250 patients with CGD over almost 40 years, the majority of whom were given diagnoses after infections of the skin, lymph node, lung, or liver. A small group of patients (approximately 5%) were identified because of inflammatory lesions being their primary clinical event. The diagnosis was usually established early in life (median age of diagnosis, 5.4 years), although a small proportion were given diagnoses as adults. Notably, the majority of these later diagnoses were due to autosomal recessive forms of CGD.

Isolation of the microorganism causing infection in patients with CGD is essential to rational and appropriate treatment but is not always feasible. In the last 10 years, 80% of patients with CGD at the NIH with a pulmonary infection underwent some type of diagnostic procedure, either needle biopsy or bronchial lavage. Of these procedures, 52% were successful in identifying a pathogen. Coinfection, such as fungal plus bacterial infection, was found in less than 10% of biopsy specimens. Viral infections

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appeared at similar rates as in the general population (unpublished data).

The majority of infections in North American patients with CGD are due to 4 bacterial organisms (*Staphylococcus aureus*, *Serratia marcescens*, *Burkholderia cepacia* complex, and *Nocardia* species), as well as species of the fungus *Aspergillus*. Invasive aspergillosis has been a major cause of morbidity and mortality in patients with CGD, but the advent of the newer azole antifungal agents has dramatically changed the treatment and outcome of these infections and shifted the intractable fungal infections to non-*fumigatus* *Aspergillus* species, dematiaceous molds, and hyalohyphomycosis, such as *paecilomyces*.<sup>1,7,8</sup>

Patients with CGD might present without symptoms or with low-grade fevers and only mild constitutional symptoms inconsistent with the extent of disease seen by using imaging studies. Consequently, frequent imaging studies (eg, computed tomography and magnetic resonance imaging) are recommended for clinical monitoring. The paradoxically dampened inflammation in response to some serious infections and the exaggerated responses to some noninfectious stimuli (see below) remain perplexing.

The lung was the most common site of disease in the NIH cohort, and *Aspergillus* species was responsible for approximately 40% of the culture-positive cases. Chest scans and markers of acute inflammation (eg, C-reactive protein and erythrocyte sedimentation rate) have proved useful in the diagnosis and monitoring of fungal disease (unpublished data). The role for serology, such as the  $\beta$ -D-glucan and galactomannan assays, are undefined in patients with CGD, but when results are positive, these assays might be helpful to follow in some cases. North American studies have identified a much higher incidence of *Burkholderia* and *Nocardia* species infections than in European reports, which in part might reflect the differences in diagnostic approaches and might also reflect environmental differences.<sup>4,9</sup>

Emerging pathogens in patients with CGD include gram-negative pathogens (eg, *Granulibacter bethesdaensis*<sup>10</sup>), gram-positive pathogens (eg *Actinomyces* species<sup>11</sup>), and fungi (eg, *Neosartorya udagawae*<sup>12</sup>). Occurrence of these uncommon pathogens in patients with CGD might provide clues to the critical pathways and functions of the NADPH oxidase.<sup>13-17</sup>

Liver abscesses are common in patients with CGD.<sup>18</sup> Thirty percent of NIH patients have had liver abscesses, with 25% of these occurring more than once. *S aureus* was the organism most frequently cultured, and surgical resection was the usual treatment. Percutaneous drainage was usually not helpful because liver abscesses associated with CGD tend to develop multiple loculations. When resected, the lesions are a collection of microabscesses.<sup>18</sup> Corticosteroids have been reported to be helpful in 2 cases of liver abscess.<sup>19</sup> Other staphylococcal infections are typically confined to the skin or lymph nodes.<sup>20</sup>

Patients compliant with prophylaxis still have skin infections, but these infrequently spread. Skin and soft tissue infections are caused by *S aureus*, *Klebsiella* species, *S marcescens*, *B cepacia* complex, and some fungi. Lymph node and skin infections have decreased overall and constitute only about 20% of the infections seen in NIH patients.

Antibacterial (trimethoprim/sulfamethoxazole) and antifungal (itraconazole) prophylaxis has significantly reduced the rates and severity of infections in patients with CGD, but breakthrough infections still occur.<sup>21-23</sup> Prophylactic antibiotics were used in 93% of NIH patients with CGD, with trimethoprim/sulfamethoxazole the most frequent. Intolerance to sulfamethoxazole or other

adverse events typically led to use of trimethoprim alone, cephalosporins, or quinolones.

Fungal prophylaxis was used by only 68% of the patients, although it was recommended for all patients with CGD. Of these, 55% were receiving itraconazole, 30% were receiving posaconazole, and 15% were receiving voriconazole. Typically, patients receiving the latter 2 agents were receiving them after having been treated for an invasive fungal infection. There are no data on patients with CGD comparing voriconazole, posaconazole, or itraconazole. A single-center transplantation study did show better outcomes with posaconazole compared with itraconazole; however, direct extrapolation to patients with CGD might not be appropriate.<sup>24</sup>

Mild toxicity related to drugs was recorded in 36% of the overall NIH cohort, 15% of whom had photosensitivity, most likely caused by voriconazole or trimethoprim/sulfamethoxazole. Severe photosensitivity leading to squamous cell carcinoma and melanoma has been reported with long-term voriconazole.<sup>25,26</sup> Patients receiving voriconazole should use aggressive sun protection. For patients with severe voriconazole-induced photosensitivity despite sun avoidance, posaconazole causes less photoreactivity.

IFN- $\gamma$  was shown in 1991 to be effective prophylaxis for CGD.<sup>27</sup> However, use in Europe has been less than in the United States because nonrandomized European data suggested less benefit from IFN- $\gamma$ .<sup>28</sup> Even in our own cohort, with the advent of better antifungal agents and more active oral antibiotics, the percentage receiving IFN- $\gamma$  is only 36% because of intolerance or lack of access. Fevers, myalgias, and irritability were reported as reasons for stopping the IFN- $\gamma$  in 13% of patients in 1 study.<sup>29</sup>

Renal failure or severe dysfunction occurred in 3.5% of our patients, probably because of long-term amphotericin exposure before the advent of newer agents.

## INFLAMMATORY COMPLICATIONS AND AUTOIMMUNITY IN PATIENTS WITH CGD

Dysregulated inflammation in patients with CGD typically occurs in response to a trigger and might be due to either increased proinflammatory or decreased anti-inflammatory mediators. Patients with CGD frequently experience inflammatory complications, and some might have autoimmune problems.<sup>30</sup>

Other than infection, a characteristic feature of CGD is granulomatous inflammation. CGD granulomas are typically noncaseating, are composed of multinucleated giant cells, and can be found in multiple organs, including the brain, lungs, liver, spleen, and gastrointestinal tract. When present in hollow viscera, they can lead to obstruction, such as obstruction of the gastric outlet or ureteral obstruction, which are relatively common in patients with X-linked CGD. For most of these granulomas, no pathogen is identified, and they respond rapidly to steroids, suggesting that the inciting event is not an invasive infectious one. Surgical intervention should be avoided, and corticosteroids, when used, are usually started at doses of 1 mg/kg/d and then tapered after 1 week. In many patients the symptoms recur when the steroid dose is reduced, and thus our current practice is to taper the corticosteroid dose gradually to around 0.1 mg/kg/d on alternate days. Patients with recurring problems can be kept on low-dose prednisone for years, which does not appear to increase infection rates or impair growth.<sup>6</sup>

A unique presentation in CGD is an acute pneumonitis caused by the inhalation of mulch or other decayed organic matter (eg,

potting soil, hay, and leaves). Exposure to a large burden of fungal elements and spores triggers an acute inflammatory response, leading to fever, hypoxia, and diffuse infiltrates, usually beginning within 1 week of the exposure.<sup>31</sup> Similar responses are seen in mice with CGD exposed to live or even dead fungi,<sup>32</sup> indicating that some of this pathology is due to dysregulated inflammation rather than infection *per se*. Bronchoscopy and lung biopsy specimens might yield 1 or more fungal pathogens, especially *Aspergillus* species. In addition to rapid institution of antifungal agents, moderately high doses of prednisone (1 mg/kg/d) help prevent respiratory failure and might facilitate more successful healing.<sup>31,33</sup>

Inflammatory lesions without demonstrated pathogens have also been noted in the lungs of patients with CGD and are characterized by discrete infiltrates on chest computed tomography that wax and wane without intervention. In some patients diffuse pulmonary inflammation can progress to hypoxia and functional limitation.<sup>34</sup> It is difficult to exclude infection despite negative cultures, cytology, nucleic acid testing, and the lack of improvement in response to antibacterial or antifungal agents. However, in some cases empiric treatment beyond corticosteroids has included methotrexate. Progressive lung inflammation with augmented nuclear factor  $\kappa$ B activation and increased proinflammatory cytokine levels has been recently demonstrated in mice with CGD (p47 and gp91<sup>phox</sup> deficient) after intratracheal challenge with zymosan or LPS.<sup>35</sup>

Inflammatory bowel disease characterized by granulomatous involvement of the bowel, especially in the perirectal area, is hard to distinguish pathologically from Crohn disease. However, the inflammatory bowel disease seen in patients with CGD is typically limited to the bowel and unassociated with any of the extraintestinal manifestations often seen in patients with Crohn disease. In the NIH series 43% of X-linked and 11% of p47<sup>phox</sup>-deficient patients had biopsy-proved symptomatic bowel disease.<sup>6</sup> How many had active subclinical disease remains unknown. Other autoimmune diseases in patients with CGD and carriers have included IgA nephropathy, antiphospholipid syndrome, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, and juvenile idiopathic arthritis.<sup>7</sup> An estimated 10% of the patients with CGD followed at the NIH have some autoimmune manifestation other than inflammatory bowel disease. The underlying cause for this predisposition to autoimmunity remains unknown. Polymorphisms in a few genes have been loosely associated with inflammatory complications in patients with CGD (MPO; mannose-binding lectin; Fc receptors IIa, IIIa, and IIIb; TNF- $\alpha$ ; and IL-1 receptor).<sup>36</sup>

Dysregulated inflammation might play a role in the development of autoimmune complications in patients with CGD. For example, normal NADPH oxidase activity plays regulatory roles in apoptosis<sup>37-39</sup> and macrophage clearance of apoptotic cells.<sup>40-42</sup> Altered NADPH oxidase function can therefore lead to aberrant macrophage programming, impaired clearance of antigen, and intracellular elements, with further recruitment of neutrophils and prolonged production of IL-8, IL-1 $\beta$ , caspases, and other proinflammatory cytokines.<sup>43,44</sup> Persistence of CGD phagocytes during induced inflammation was reported in human X-linked CGD<sup>45</sup> and in murine CGD-related peritonitis.<sup>46,47</sup> These diverse studies suggest that the role of the NADPH oxidase in patients with CGD extends far beyond the simple predisposition to infection.

Treatment for inflammatory and autoimmune complications in patients with CGD is problematic because most agents are

immune suppressive and immunity is already impaired in patients with CGD. Many patients respond well to corticosteroids, but they might require prolonged courses. Sulphasalazine and azathioprine are useful steroid-sparing agents. TNF- $\alpha$  inhibitors, such as infliximab, are effective anti-inflammatory agents but might significantly increase the risk of severe and even fatal infections.<sup>48</sup> The risk of infection needs to be weighed carefully against the risks of uncontrolled mucosal inflammation or surgery that might be further complicated by persistent inflammation, abscesses, and fistulae formation at surgical sites. If TNF- $\alpha$  inhibitors are used, augmented prophylaxis and enhanced vigilance regarding exposures are mandatory. Methotrexate and hydroxychloroquine (Plaquenil) can be effective in those with arthritides or lupus-like problems.

## HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR PATIENTS WITH CGD

Currently, the only known cure for CGD is allogeneic hematopoietic cell transplantation. Historically, this has only been reluctantly offered because of the risks of procedure-related morbidity and mortality. Additionally, unrelated donor transplantations were riskier than sibling transplantations, and the pool of donors was limited. From 1973, when the first CGD bone marrow transplant was performed, until now, the results of 99 transplantations, not including cord blood recipients, have been published, with the majority being single-case reports.<sup>49-70</sup> However, of the 99 patients undergoing transplantations, 50 occurred in the last 10 years compared with 49 in the prior 27 years. With the advent of nonmyeloablative regimens, the risks surrounding transplantation have decreased and have permitted transplantation in patients with ongoing infections. Additionally, more transplantations are being performed with unrelated donors. Notably, the first transplantation ever performed for CGD used an unrelated donor, and to date, 22 patients have undergone transplantation with unrelated donor transplants, with the majority performed within the last 10 years.

Hematopoietic stem cell transplantation has been more frequently offered to European patients with CGD than North American patients. The first large report of bone marrow transplantation for CGD was from a group of European centers describing the results in 27 patients undergoing transplantation from 1985 to 2000 (7 of whom were described previously in single-case reports).<sup>65</sup> HLA-matched sibling donors were used for 25 of these cases, and the majority received a myeloablative, busulfan-based regimen. In 9 patients undergoing transplantation during a refractory infection, there were 2 graft failures and severe graft-versus-host disease (GvHD) in 3 patients, with 1 patient dying as a result.

In the largest North American study published to date, Horwitz et al<sup>69</sup> reported the outcomes of 10 patients who received a fully matched sibling donor transplant with a nonmyeloablative conditioning regimen of fludarabine, cyclophosphamide, and antithymocyte globulin (ATG). Stem cell products were T-cell depleted, and donor lymphocyte infusions were given after transplantation to augment engraftment. Eight patients were engrafted, but 1 had significant GvHD resulting in death, with 1 additional patient dying 18 months after transplantation with pneumococcal sepsis despite full myeloid engraftment. Of the nonengrafted patients, both survived and went on to retransplantation, with 1 dying subsequently. Long-term follow-up in the engrafted patients showed

stable mixed chimerism in 2 patients, including donor lymphoid engraftment of less than 50% in 1 patient but continued myeloid engraftment, with more than 10 years' follow-up. All surviving patients with engraftment remain phenotypically well, with no evidence of CGD-related autoimmune complications or infections.

In 2009, a survey of North American centers treating patients with CGD performed in conjunction with the Center for International Blood and Marrow Transplant Research found 59 patients had undergone allogeneic transplantation for CGD, with 71% survival overall. Three of these patients had survived beyond 10 years, but outcome data were not published. As transplantation methods have changed, efforts are underway to comprehensively compile the North American CGD transplantation experience both retrospectively and prospectively.

Two other large single-center studies were recently published, both from European centers. Soncini et al<sup>70</sup> described the results in 20 patients undergoing transplantation from 1998 to 2007, one of whom was previously reported as a single-case study. Patients ranged in age from 15 months to 21 years. Ten of those were with matched sibling donors, 9 receiving bone marrow and 1 receiving cord blood. The remainder received transplants from matched and single mismatched unrelated donors, including 1 cord blood transplantation. The follow-up ranged from 4 to 117 months; 18 (90%) patients survived with continued normal neutrophil function, and 2 died from pretransplantation fungal infections. The majority of the patients received a busulfan/cyclophosphamide conditioning regimen, with alemtuzumab added for those receiving unrelated donor products.

Schuetz et al<sup>62</sup> also reported 12 patients, 9 of whom received grafts from unrelated donors. The majority received busulfan/cyclophosphamide with or without either ATG or alemtuzumab. Two patients had graft failure, and 5 patients had grade 1 or 2 acute GvHD. At a mean follow-up of 53 months, 9 of the 12 were alive, including 7 of the 9 recipients of matched unrelated transplants, all with stable engraftment, including 1 patient with mixed chimerism.

Most recently, a European consortium reported good engraftment rates and minimal GvHD by using a nonmyeloablative busulfan- and fludarabine-based regimen for both matched related and matched unrelated donors. The intravenous busulfan dose was targeted to achieve an area under the curve of between 45 and 65 mg/h, and either ATG or alemtuzumab was added along with mycophenolate mofetil for GvHD prophylaxis. Of their 24 patients, 9 had matched unrelated donors. Eight patients had grade 1 acute GvHD, 1 patient had grade 2 GvHD, and 1 patient had chronic GvHD of the skin only, which responded to treatment. Their only death after transplantation was due to pneumonia, resulting in an overall survival to date of 96%.<sup>71</sup>

Preliminary data from the NIH also suggest that intravenous busulfan should be an integral part of transplant conditioning for patients with CGD. The doses used at NIH were lower than used by Gungor et al,<sup>71</sup> at least based on the AUCs measured. Fludarabine was not a part of the regimen but alemtuzumab was. Total-body irradiation (300 cGy) was also administered to patients receiving unrelated donor grafts. Eleven patients were described by the NIH; 9 received unrelated donor products, and patients ranged in age from 3 to 32 years. There was 1 failure to engraft using an unrelated cord blood product, and late graft rejection occurred in 1 patient who received an unrelated donor product. The remainder had almost 100% myeloid engraftment, with excellent NADPH oxidase function. There were only 2 patients with GvHD, both in the

skin (1 grade 1 and 1 grade 2). One patient died from renal dysfunction unrelated to transplantation, and the rest are alive and well, including both patients with graft failure, resulting in an overall survival of 10 (91%) of 11. Notably, 9 of the 11 patients had ongoing infection at the time of transplantation, and 4 received granulocyte transfusions during the peritransplantation neutropenic period.<sup>72</sup>

The first cord blood transplantation for CGD was an 8-year-old boy undergoing transplantation with an unrelated donor matching at 5 of 6 loci published in 1999 by Nakano et al.<sup>73</sup> He was conditioned with 10 Gy of total-body irradiation, ATG, and cyclophosphamide but died at day 51 from infection. Seven subsequent patients have been reported as having received cord blood products, either from related or unrelated donors.<sup>54,64,70,74-77</sup> Three of the patients have required second transplantations. One patient received his initial cord blood product for his retransplantation. All appear to have done well, even when a cord product was used for both transplantations. More recently, with advanced genetic and fertility techniques, 3 cases of preimplantation selection have resulted in live births of siblings who have provided cord blood, bone marrow, or both. The patients who received these products appear to be doing well.<sup>78,79</sup>

## DISCUSSION

Allogeneic stem cell transplantation for CGD is becoming more common and reflects increased overall success. Survival has increased from approximately 85% before 2000 to 90% to 95% based on recently reported outcomes and our own results, even with the use of unrelated donors. In fact, outcomes with perfectly HLA-matched unrelated donors appear to approach, if not equal, those using HLA sibling donors. This suggests that donor availability should not be limiting for transplantation in patients with CGD (see Table I).

Even for those without a matched unrelated donor, cord blood products are proving to be a reasonable alternative and are being used more frequently. Even in adults, double cord products have had good engraftment rates, at least in the setting of leukemia.<sup>80</sup> In 1 study the nonrelapse mortality was slightly higher for recipients of double cord products compared with those receiving matched unrelated or matched related donor products. Studies will be needed in patients with CGD to determine whether a double cord transplant is preferable to an unrelated donor transplant.<sup>81</sup> Although 1 published case used a haploidentical donor, the patient experienced rejection, requiring a second transplantation.<sup>54</sup>

Both peripheral blood stem cells and marrow have been used successfully, and the choice for patients with CGD currently depends on donor and center preferences. Data from transplantation in patients with aplastic anemia suggest that bone marrow products result in less GvHD; however, cell dose can be a limiting factor.<sup>82</sup> Older patients with CGD often have splenomegaly, hepatomegaly, or both, thereby requiring a larger cell dose. Although T-cell depletion of products has been used in transplantations for patients with CGD, the incidence of GvHD with donor lymphocyte infusion is significant, as seen in the first NIH series.<sup>69</sup> *In vivo* or *in vitro* T-cell depletion with alemtuzumab appears to result in less GvHD without significantly affecting engraftment, although the need for viral monitoring is prolonged.

Some transplantation centers prefer myeloablative transplantation regimens.<sup>65</sup> Although graft rejection is more likely with a reduced-intensity conditioning regimen, the risk of GvHD, particularly acute GvHD, and regimen-related toxicity appears to be



TABLE I. Outcomes of transplantation in the largest studies to date

Reference	Year*	No. of patients	Unrelated	Related	Conditioning regimen (no. of patients per regimen)	GvHD prophylaxis	No. of patients with aGVHD <2	No. of patients with aGVHD >2	cGVHD	Overall survival; causes of death†	DFS
Seger et al <sup>65</sup>	2002	27	2	25	MA(17): Bu/Cy MA(1): Bu/Mel/ alemtuzumab MA(1): Bu/Cy/ATG MA(1): Bu/Cy/TNI MA(1): Bu/Cy/TT/ATG MA(1): Bu/Flu/ATG NMA(2): Bu/Flu ATG NMA(1): Flu/Cy/ATG NMA(1): Flu/TBI	Cyclosporine (27) Methotrexate (13) Prednisone (4)	3	4	3	23/27; Multiorgan failure, pneumonia and GVHD, pneumonia, nonengraftment with <i>Aspergillus</i> species and VOD	22/27
Horwitz et al <sup>69</sup>	2001	10	0	10	NMA: Cy/Flu with ATG and donor lymphocyte infusions	Cyclosporine	3	1	2	7/10; Graft failure with retransplantation, pneumococcal pneumonia, GVHD with fungal infection	6/10
Soncini et al <sup>66</sup>	2009	20	10	10	MA(16): Bu/Cy, ± alemtuzumab§ MA(1): Bu/Mel/ Campath1-G NMA(2): Flu/Mel/ Alemtuzumab NMA(1): Bu/Flu/ Alemtuzumab	Cyclosporine	5	0	3	18/20; Fungal infection	18/20
Schuetz et al <sup>62</sup>	2009	12	9	3	MA/MSD(4): Bu/Cy MA/MUD(6): Bu/Cy/ Flu + alemtuzumab or ATG MA/MUD(2): Flu/Mel/ RIT‡ ?/MUD(1): Flu/TBI	Not reported	5	0	2	9/12; Chronic GvHD, ARDS, BK virus	7/12
Gungor et al <sup>71</sup>	2010	24	9	15	NMA: dose adjusted IV Bu, Flu, alemtuzumab	Mycophenolate	9	0	0	23/24; Pneumonia	22/24
Kang et al <sup>72</sup>	2011	11	9	2	NMA: IV Bu, Alemtuzumab ± 300 cGy of radiation§	Rapamycin	2	0	0	10/11; Refusal to continue dialysis	8/11

aGVHD, Acute GvHD; ARDS, acute respiratory distress syndrome; Bu, Busulfan; cGVHD, chronic GvHD; DFS, disease-free survival; Cy, cyclophosphamide; Flu, fludarabine; MA, myeloablative; Mel, melphalan; MSD, matched sibling donor; MUD, matched unrelated donor; NMA, nonmyeloablative; RIT, radioimmunotherapy; TBI, total-body irradiation; TNI, total nodal irradiation; TT, thiotepa; VOD, veno-occlusive disease.

\*Year published.

†Each cause listed per patient.

‡Radioimmunotherapy = anti-CD66 Yttrium-90-labeled antibody (17 Gy).

§For unrelated donor recipients.

reduced with the nonmyeloablative regimens.<sup>83-85</sup> This type of conditioning also allows transplantation during ongoing infection, with fewer infection-related deaths. Furthermore, those who experienced rejection after receiving reduced-intensity conditioning have for the most part gone on to successful second transplantations. On the other hand, patients with McLeod syndrome (Kell antigen deficiency caused by contiguous gene deletion of XK, which is found next to the *CYBB* gene that encodes the gp91<sup>phox</sup>) who have red cell antigen sensitization should be considered for a myeloablative regimen or at least pretreatment with rituximab to limit red cell incompatibility because the availability of McLeod matched blood is extremely limited. Elimination of B cells with anti-CD20 therapy before transplantation diminishes the risk of transfusion reactions and makes red cell management easier during the transplantation period before conversion to donor blood type.<sup>51</sup> Those without preexisting red cell antibodies, however, have successfully undergone nonmyeloablative transplantation.<sup>64</sup> Most successful regimens in patients with CGD appear to include busulfan. Some consider fludarabine necessary as well; however, the experience at NIH does not support this.

The question remains: Which patients with CGD should undergo transplantation? Given the current success rates, some favor transplantation in all patients with CGD who have an appropriate donor at the earliest opportunity. The recent data from Kuhns et al<sup>3</sup> showed that patients with very low superoxide production had worse long-term survival than those with higher levels of NADPH oxidase activity notable particularly for the onset of increased mortality after age 20, suggesting that these patients should be considered appropriate candidates for early transplantation, particularly if a sibling matched donor is available. However, even within this subgroup, there are patients who do relatively well for prolonged periods. An increased alkaline phosphatase level, a history of liver abscesses, and a decrease in platelet count reflecting portal hypertension are adverse prognostic indicators.<sup>86</sup> These patients might also be considered for early transplantation.

Even with improved survival and longevity caused by better infection and inflammation management, complications and their consequences can accumulate over time. However, transplantation outcomes are probably better before infectious and inflammatory damage accumulates. Transplantation has reversed some

of the inflammatory and autoimmune complications associated with CGD and might prevent their development.<sup>65</sup> Therefore patients with significant inflammatory or autoimmune disease should also be at least evaluated for transplantation, preferably at a center with experience in CGD transplantation. Those who have an active infection should not be summarily excluded because nonmyeloablative regimens have been successful, even in this setting. Additionally, granulocyte transfusions might be helpful during the transplantation period for those with active infections and do not appear to affect engraftment.<sup>87</sup> For those with a prior history of infections, including fungal infections but no active infection, the necessity to use granulocytes is not clear. Patients who are being considered for transplantation should not receive granulocytes before transplantation (as opposed to during) so as to avoid the development of HLA alloimmunization.

Although overall CGD life expectancy is still less than that in the general population, even with the best current care, the strides in infection and inflammation management over the last decades have been significant. Allogeneic hematopoietic transplantation might have unanticipated consequences, and even the reduced-intensity regimens might pose unknown long-term risks. Although there has been strong interest and progress in gene-based therapies, it has not been shown to be curative at this point and has been reviewed elsewhere.<sup>88</sup> Further, even *ex vivo* gene therapy appears to require some form of conditioning, and therefore cytoreductive agents might still be needed.<sup>89-91</sup>

However, allogeneic transplantation has also improved dramatically over the last decade because of improved conditioning regimens and GvHD prophylaxis, high-resolution sequence-based matching, and improved pretransplantation, peritransplantation, and posttransplantation management. It has become a successful and sensible option for many patients with CGD that will likely treat and prevent both infectious and inflammatory complications. Although further studies will be required to determine optimal timing, donor selection, and long-term efficacy in these patients, hematopoietic stem cell transplantation is finally coming of age as a curative treatment for CGD.

#### What do we know?

- Patients with CGD with very low NADPH superoxide production have worse outcomes overall.
- Conservative treatment has improved, including improved diagnosis, infection, and inflammatory management.
- CGD, including inflammatory or autoimmune complications, can be cured with hematopoietic transplantation.
- Nonmyeloablative transplantation regimens can be effective for patients with CGD.

#### What is still unknown?

- Which patients are at risk for inflammatory versus infectious complications?
- What is the best management for the autoimmune complications of CGD?
- Who would benefit most from allogeneic transplantation, and who would not?
- What are the long-term outcomes of hematopoietic transplantation?

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